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Docket No. 47653.1 (1789)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	J.C. Houck, et al.		
Serial Number:	09/189,130	Art Unit:	1631
Filed:	November 10, 1998	Examiner:	M. Borin
For:	SMALL PEPTIDES AND METHODS FOR TREATMENT OF ASTHMA AND INFLAMMATION		

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231 on December 4, 2000.

Barbaranne Jenness

Barbaranne Jenness

Honorable Commissioner for Patents
Washington, DC 20231

Sir:

DECLARATION OF JAMES CLAGETT

I, James Clagett, hereby declare that:

1. I am a citizen of the United States of America residing at 5615 139th Avenue SE, Snohomish, Washington 98290 and I am one of the Applicants in the above application.

2. I hold a Ph.D. in microbiology from the University of Nebraska. I have over 30 years experience in research and development related to microbiology, particularly in the fields of immunology and immunopathology. A copy of my curriculum vitae is

attached hereto as Attachment A.

3. Since 1997, I have been a consultant providing scientific expertise to the biotechnology and pharmaceutical communities.

4. I personally performed or directly oversaw the experiments which produced the results presented and discussed herein.

5. I have read and understand the Office Action of June 28, 2000, including the references cited therein.

6. The present invention is directed to a pharmaceutical composition having anti-inflammatory activity comprising a pharmacological carrier and an anti-inflammatory effective amount of a peptide having the formula f-Met-Leu-Phe-Phe.

7. Based on my knowledge and experience in the field, it is my opinion that, prior to the present invention, it was well known to those skilled in the art that formyl methionyl peptides have pro-inflammatory activity.

8. However, surprisingly, we have discovered that f-Met-Leu-Phe-Phe, can provide a useful anti-inflammatory effect.

9. In the Office Action dated June 28, 2000, the examiner states:

> . . . the essential difference [is] the effect of a biological mediator (such as F-Met peptide) when it is used alone as compared to its use in the presence of another pro-inflammatory agent. Cellular response to f-Met peptides (which can be described as inflammatory response) is the same type of reaction which mediates response of the organism to a foreign infection. It is well known in the art that biological mediators such as chemotactic factors stimulate the migration of neutrophils from circulation into sites of infection or tissue damage. These mediators are also believed to increase cell adhesion to injured sites and to activate neutrophils to release toxic agents such as oxygen metabolites and proteases. Thus, in the presence of a provoked infection the response caused by f-Met peptides have protective, anti-inflammatory function.

10. It is true that the prior art teaches that:

> Cellular response to f-Met peptides (which can be described as inflammatory response) is the same type of reaction which mediates response of the organism to a foreign infection. It is well known in the art that biological mediators such as chemotactic factors stimulate the migration of neutrophils from circulation into sites of infection or tissue damage. These mediators are also believed to increase cell adhesion to injured sites and to activate neutrophils to release toxic agents such as oxygen metabolites and proteases

However, those responses are "pro-inflammatory" responses. The claimed composition of the present invention blocks those responses. Thus, the claimed composition has an "anti-inflammatory" response.

11. The examiner also states and concludes that:

> Characteristically, . . . the effect of the claimed composition is demonstrated only as inhibitor of inflammatory effect caused by another f-Met peptide, fMLP. The absence . . . of showing of the effect of fMLPP alone is not surprising because Kermode shows (Table 2) that fMLPP (the peptide of the claimed composition) is more potent chemotactic agent and stimulator of neutrophil degranulation than fMLP (the peptide used as "pro-inflammatory" agent). One would expect that fMLPP, alone, would be at least as "pro-inflammatory" as fMLP.

12. However, Kermode conducted *in vitro* tests using rabbit neutrophils that were suspended in solution containing salts, BSA, buffer and for some tests glucose. We have found that such *in vitro* tests are not a predictor of the bioactivity of fMLPP *in vivo*. Although based on the teachings of the prior art, " [o]ne would expect that fMLPP, alone, would be at least as 'pro-inflammatory' as fMLP," as concluded by the examiner, that is an erroneous expectation. Further, based on the teachings of the prior art, one of ordinary skill in the art would not expect fMLPP to act any differently after prior treatment with fMLP.

13. To satisfy the examiner's curiosity about the effect of fMLPP alone, the following experiments have been performed under my direction and control.

Briefly, (i) 200 µg of fMLP alone; (ii) 200 µg fMLPP (HK-X) alone; (iii) 200 µg of fMLP and 200 µg of HK-X administered simultaneously; and (iv) as a control the vehicle of HK-X (4% DMSO in Tyrode's solution) each were injected subcutaneously into the dorsum of the feet of female Balb/CJ female mice. Animals were sacrificed at 30 minutes post-injection and the feet collected for histological examination. The cutaneous soft tissues were dissected from the bones, fixed in 10% (v/v) neutral buffered saline and embedded in paraffin. Five – seven micron sections were cut and stained with H&E for the detection of cellular content and location within the muscularis and dermis. The numbers of neutrophils in the extravascular zone, occupying 2,200 u^2 around blood vessels, were counted. For each specimen, a total of 10 vessels were counted. The means and SE are presented. Differences between groups were determined by one-way ANOVA followed by the appropriate post hoc tests

using SigmaStat version 2.0 software (SPSS Inc., Chicago, IL). The results are illustrated in the figures attached hereto.

14. Figure 1 shows the polymorphonuclear cell count outside the vessels, 30 minutes after injection of 200 µg fMLP alone; 200 µg fMLP and 200 µg HK-X together; 200 µg HK-X alone; and vehicle alone, into the subcutaneous tissues of the dorsum of mice feet.

- Injection of 200 µg of fMLP alone resulted in 24 neutrophils per 2,200 u^2 in the intercellular matrix.
- In specimens from treatment with HK-X alone, results were substantially identical to the control (vehicle treatment alone) ($p<0.05$).
- The simultaneous exposure of fMLP and HK-X resulted in a 91 % **inhibition** of neutrophils diapedesis compared to fMLP alone ($p<0.05$).

15. Figure 2 is a microphotograph comparing stained tissue sections harvested from mice 30 minutes after injection with (i) 200 µg of fMLP alone, (ii) 200 µg fMLP and 200 µg HK-X simultaneously and (iii) 200 µg of HK-X alone into the subcutaneous layers of the skin on the dorsum of mice feet.

- Panel A shows the results of injection of 200 µg of fMLP alone. FMLP treated mouse skin shows the influx of the neutrophils in the surrounding areas of the blood vessel (BV). The neutrophils are located in the connective tissue area (Arrows).

- Panel B shows the results of 200 µg fMLP and 200 µg HK-X when injected simultaneously. The mouse skin shows no cellular infiltration at the surrounding areas of the blood vessel (BV). Occasionally, neutrophils are seen. (Arrows).
- Panel C shows the results of injection of 200 µg of HK-X alone. The treated mouse skin shows no changes in connective tissues and the surrounding area of the blood vessel (BV).

16. Figure 3 shows a higher power examination of specimen similar to those in figure 2.

- Panel A shows the subcutaneous tissue of an HK-X treated mouse. The subcutaneous tissue is normal. The blood vessels (BV) show no neutrophils. Only occasionally a neutrophil is observed (Arrow).
- Panel B is the vehicle control treated mouse. The subcutaneous tissue shows no sign of the effect of a vehicle solution injection.
- Panel C shows the results of 200 µg fMLP and 200 µg HK-X when injected simultaneously. The subcutaneous tissue shows very little change in the histology except for a few neutrophils attached on the endothelial cell surface (Arrow heads). Neutrophils are observed but in very little numbers as compared to the fMLP treated skin tissue (Panel D).
- Panel D shows the results of shows the results of injection of 200 µg fMLP alone. The subcutaneous tissue was heavily infiltrated with

neutrophils 30 minutes after injection of fMLP as seen in the surrounding area of the blood vessel (BV). Many neutrophils are also seen attached to the surface of endothelial cells.

17. Based on my knowledge and experience in the art, from these experiments, it can be concluded that fMLP (prior art) administration into the skin of mice produced an intense accumulation of polymorphonuclear cells, largely neutrophils. In contrast, fMLPP (HK-X) has no significant effect when administered alone. However, in connective tissues HK-X administered simultaneously with an equal amount of fMLP totally prevented the accumulation and diapedesis of polymorphonuclear cells into interstitial spaces while administration of HK-X alone showed no inflammatory recruitment of polymorphonuclear cells or other inflammatory cells in the connective tissues. It can also be concluded that HK-X blocks the earliest events triggered by fMLP in the inflammation cascade, that is, recruitment of inflammatory cells.

18. It is my understanding that the Examiner contends that, based on Kermode et al, "one would expect that fMLPP, alone, would be at least as "pro-inflammatory" as fMLP." The above described experiments show the opposite result, that is, fMLPP is anti-inflammatory and also inhibits the pro-inflammatory effects of fMLP.

19. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true;

and, further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Codes, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

11-21-00
Date

James Clagett

FIGURE 1

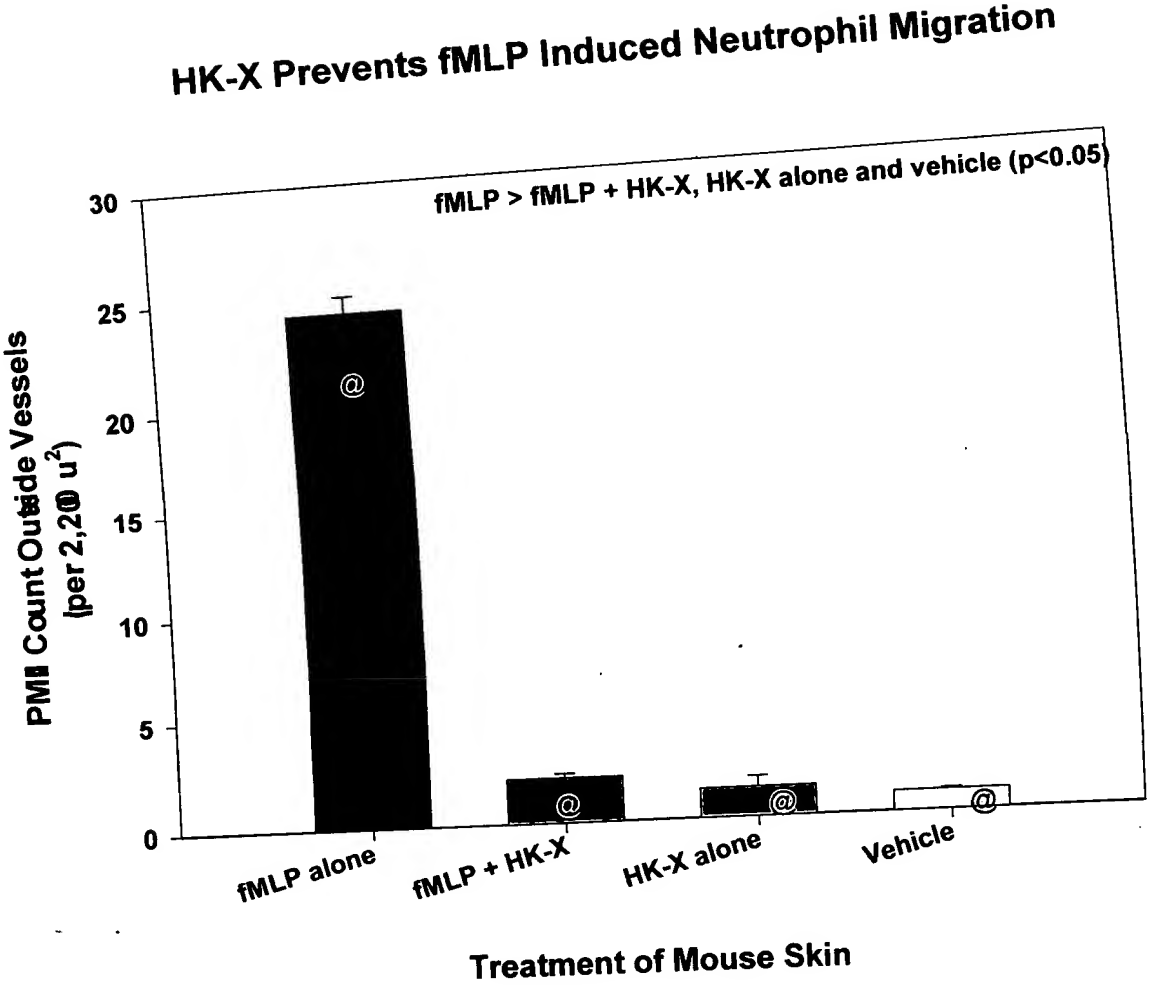

HK-X Prevents fMLP Induced Neutrophil Migration
fMLP > fMLP + HK-X, HK-X alone and vehicle (p<0.05)
PMN Count Outside Vessels
(per 2,200 u²)
30
25
20
15
10
5
0
@
@
@
@
fMLP alone
fMLP + HK-X
HK-X alone
Vehicle
Treatment of Mouse Skin

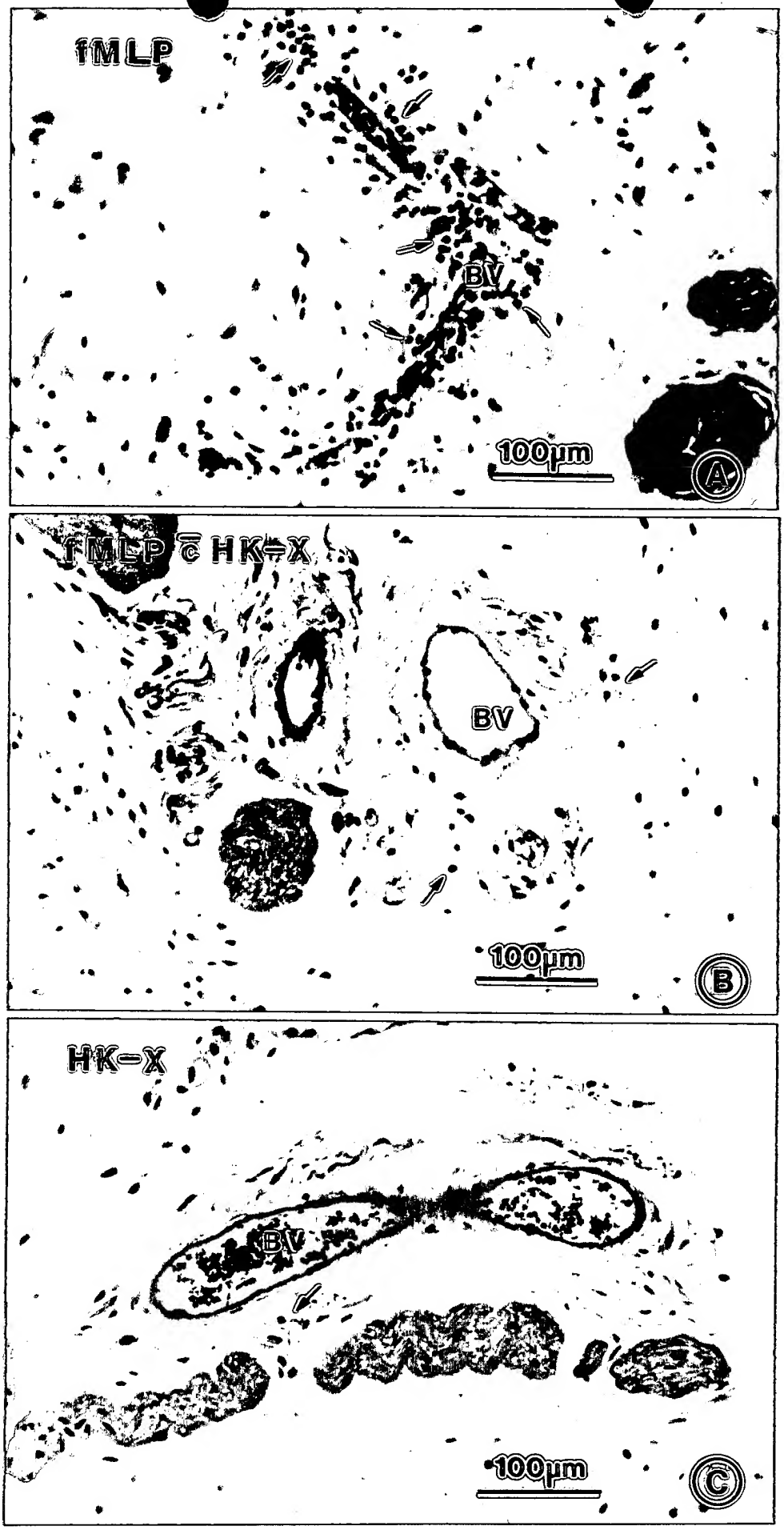
Figure 2

Micrographs to illustrate the treatment reaction in skins of mice.

A). fMLP treated mouse skin shows the influx of the neutrophils in the surrounding areas of the blood vessel (BV). The neutrophils are located in the connective tissue area (Arrows).

B). A fMLP and HK-X treated mouse skin shows no cellular infiltration at the surrounding areas of the blood vessel (BV). Occasionally neutrophils are seen (Arrows).

C). HK-X treated mouse skin shows no changes in the connective tissues and the surrounding area of the blood vessel (BV).


fMLP
BV
100μm
A
fMLP & HK-X
BV
100μm
B
HK-X
BV
100μm
C

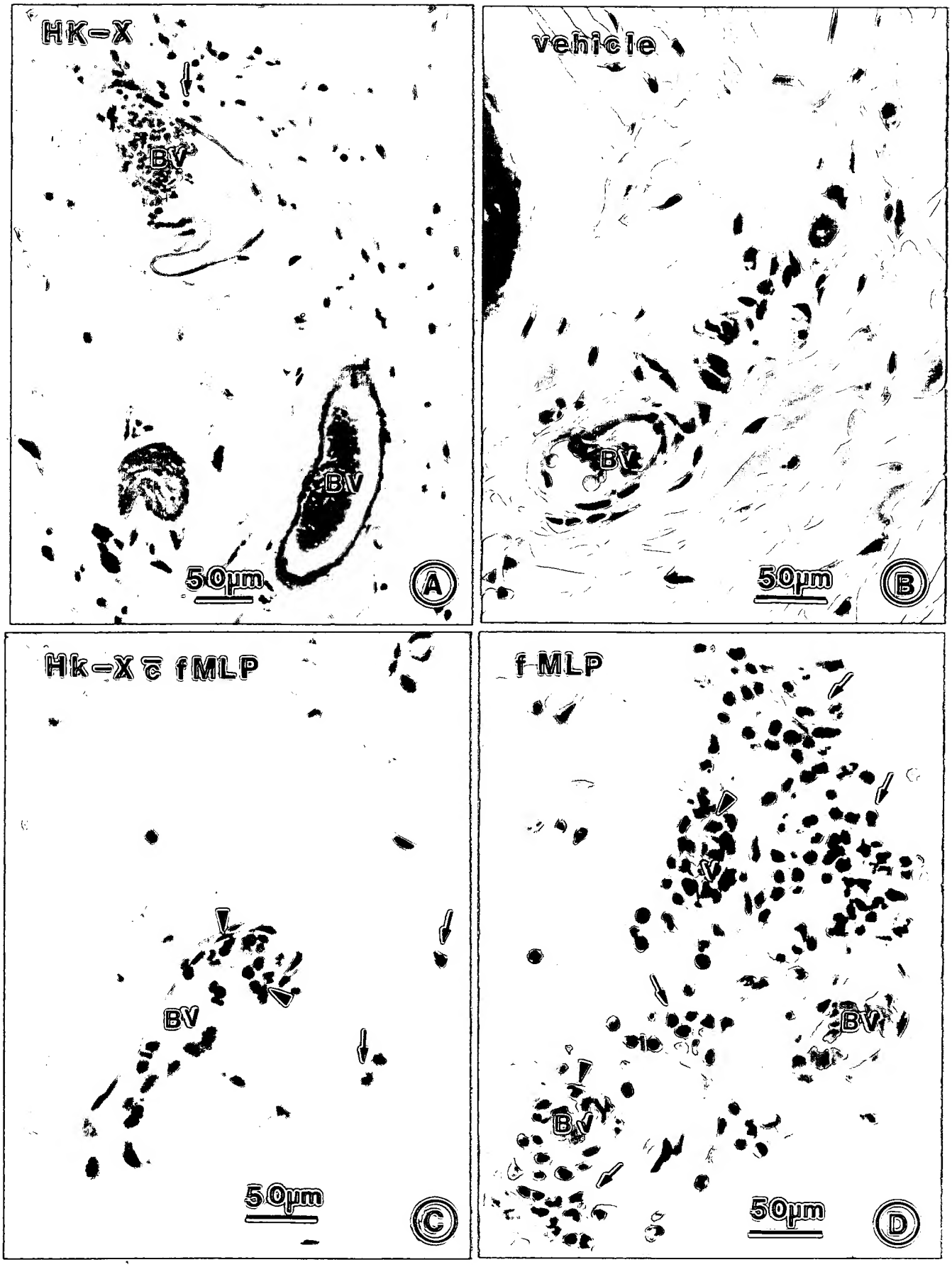
Figures 3

A). A HK-X treated mouse skin shows the normal appearances of the subcutaneus tissue. The blood vessels (BV) show no neutrophils. Only occasionally the observation of neuphil present (Arrow).

B). A vehicle control mouse skin shows no sign of the effect of vehicle solution injection.

C). A HK-X and fMLP treated mouse skin shows very little change in the histology except a few neuphils are attaching on the endothelial cell surface (Arrow heads). Nuetrophils are seen but in very little number as compared to the fMLP treated skin tissue (see Fig. D)

D). A fMLP treated mouse skin shows the aboundant number of neutrophils present in the surrounding area of the blood vessel (BV).
Many neutrophils are also seen attached to the surface of endothelial cells.


HK-X
BV
BV
50μm
A
vehicle
BV
50μm
B
Hk-X ⊂ fMLP
BV
50μm
C
fMLP
BV
BV
50μm
D

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EXPERIENCE:

CLAGETT CONSULTING
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SNOHOMISH, WASHINGTON, 98290

Founder and Partner: January 1, 1997 to present.

Providing quality expertise to the biotechnology and pharmaceutical communities. Lead an assembled group of individuals with experience in regulatory affairs, preclinical and clinical studies. The team has worked together for an average of 3 years and was instrumental in bringing products from research through production for GenSci Regeneration Laboratories Inc., Irvine, CA. Current list of clients includes Histatek, LLC, San Francisco, CA and BioTherapeutic Computers, Seattle, WA.

BIOCOLL LABORATORIES INC.
562 1ST AVENUE SOUTH
SEATTLE, WASHINGTON, 98104

Vice President and Scientific Director: January 1993 to August 1, 1997.

Responsible for implementing and maintaining the company's overall scientific plan.
Initiated the development of the company's first product, the Tissue Bone Matrix sponge and the DynaGraft family of products and human banked tissue. Supervised the writing and implementation of the Standard Operating procedures or the TBM sponge. Initiated the scientific research of new products and managed numerous consultants supporting the company's scientific strategic plan. Carried the company from conceptual design of products through introduction to the marketplace including continuous interaction with FDA.

DENTAL DIAGNOSTIC SERVICES
2000 116TH AVENUE NE.
BELLEVUE, WASHINGTON 98004

Founder and Officer: December 1992 through January 1, 1993

Responsible for taking the company from no revenues to profitability in one year. Company had over 450 clients using the sterility testing services of Dental Diagnostic Services.

THE DENTAL RESOURCE INC.
2000 116TH AVENUE NE,
BELLEVUE, WASHINGTON 98004

Consultant: October 1990 to December 1992

Responsible for developing product concept for novel water filtration device for dental offices. Participated heavily in selling devices to dental practitioners.

ULTRA DIAGNOSTICS CORPORATION
4526 11th Avenue NE, Seattle, Washington, 98108

Chief Executive Officer, President, and Scientific Director: December 1988 to December 1989.

Responsible for implementing and maintaining the company's overall business plans. Maintained on-going communications with investors. Supervised the recruitment of research and development personnel and management finance, administration, marketing and regulatory functions. Responsible of business development where a contract of $500,000 for research and development of new reagents was concluded. Responsible for continued venture funding of approximately $900,000. Maintained ongoing contact with key administrative and upper management individuals of the biotechnology and academic sectors in the Northwest.

President and Scientific Director: December 1984 to December 1988. Implemented the company's research and development plans and assisted the Chief Executive Officer with business development functions where research and development contracts worth $500,000 were secured. Coordinated the use of the Scientific Advisory Board and recruited and hired key scientific personnel. Assisted the Chief Executive Officer in capital formation from "seed" through venture financing. The capital raised was in excess of $4 million.

UNIVERSITY OF WASHINGTON
Schools of Medicine and Dentistry
Seattle, Washington, 98105

Affiliate Professor: 1987 to 1989.

Taught a course in Immunology and Immunopathology to Graduate Dental Students.

Professor of Periodontics and Microbiology and Immunology: 1983 to 1987

Associate Professor of Periodontics and Microbiology and Immunology: 1978 to 1983.

Research Assistant Professor of Periodontics and Microbiology and Immunology: 1973 to 1978

Taught graduate and undergraduate Immunology and Immunopathology to Microbiology and Immunology majors as well as participated in team teaching to dental and medical students. Received well above average reviews of teaching skills by students. Maintained a research laboratory with technicians, 2 doctoral and 6 masters' students. Obtained research support averaging $150,000 per year and served on the Faculty Senate and the Human Subjects Review Committee. Served as a member on 15 doctoral and masters thesis committees.

PROFESSIONAL ASSOCIATIONS:

Editorial Board of Journal of Dental Research
Biomedical Research Support Grant Committee
American Association of immunologists
Sigma Xi

EDUCATION:

Scripps Clinic and Research Foundation	Postdoctoral Fellowship	1973
University of Nebraska	Ph.D.	1970
DePauw University	BS	1964

PUBLICATIONS

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